REMARKS

After entry of this amendment, claims 1-15 are pending. The claims have been amended without disclaimer or prejudice to better comply with U.S. practice and find support *inter alia* in the original claims. No new matter has been added.

The abstract has been amended as suggested by the Examiner. No new matter has been added.

Objection to the Abstract

The Examiner objected to the abstract for the recitation of the term "said." In light of the amendments, the objection is rendered moot. Withdrawal of the objection is respectfully requested.

Rejection Under 35 U.S.C. 103(a)

Wilms in view of Moralejo

Claims 1-11 and 13-15 are rejected as being obvious under 35 U.S.C. § 103(a) over Wilms *et al.* (2001; hereinafter "Wilms") in view of Moralejo *et al.* (1993; hereinafter "Moralejo"). Applicants respectfully traverse and urge reconsideration of the rejection for the following reasons.

The Examiner bears the initial burden of establishing *prima facie* obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). Further, to support a *prima facie* conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. See *In re Lowry*, 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994); see also *Ex parte Alexander*, 86 USPQ2d 1120, 1122 (BPAI 2007) (where the Board reversed the obviousness rejection in part because the Examiner had not identified all the elements of the claim).

The Examiner characterizes Wilms as allegedly teaching host cells having the L-rhamnulose kinase (RhaB) gene inactivated which would reduce consumption of the expensive

inducer L-rhamnose and where the cells are used to produce a heterelogous polypeptide enzyme. The Examiner acknowledges that Wilms does not teach inactivation of the L-rhamnose isomerase gene in the host cell. The Examiner relies on Moralejo for allegedly teaching the gene cluster encoding enzymes for L-rhamnose metabolism in *E. coli* and that inactivation of rhamnose isomerase would be expected to block any catabolism of L-rhamnose.

Moralejo does not remedy the deficiencies of Wilms. Moralejo describes identification of the open reading frames corresponding to rhaB, rhaA, and rhaD by sequencing of a fragment complementing mutations in the structural genes (Moralejo, abstract). Moralejo further discloses that only the rhaB leader region functions as a promoter and that mutations in the genes were used to show that L-rhamnose may directly induce rhaBAD transcription. *Id.* Thus, Moralejo does not teach or suggest a method for expressing nucleic acid sequences in prokaryotic host cells or a host cell which is deficient with regard to L-rhamnose isomerase which comprises a DNA construct comprising a nucleic acid to be expressed under the transcriptional control of an L-rhamnose-inducible promoter where the promoter is heterologous with the nucleic acid as required by the claims. Further, Wilms does not teach inactivation of the L-rhamnose isomerase gene in the host cell, as acknowledged by the Examiner, and Wilms also does not teach a host cell which is deficient with regard to L-rhamnose isomerase as required by the claims. Because Wilms and Moralejo, alone or in combination, do not teach or suggest all the claim limitations, a *prima facie* case of obviousness has not been established.

The Examiner concludes that it would be obvious to modify the method of Wilms by inactivating the RhaA gene rather than the RhaB gene to greatly reduce the amount of L-rhamnose needed. Applicants strongly disagree.

It is well established that under 35 U.S.C. § 103 the Examiner must consider the reference in its entirety, *i.e.* as a whole, including portions that teach away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); see also *KSR*, 127 S. Ct. at 1740; MPEP § 2141.03 (VI). It is improper to combine references where the references teach away from their combination. *See* MPEP § 2145 (X)(D)(2) (citing *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). In addition, the Examiner cannot selectively pick and choose from the

disclosed parameters without proper motivation as to a particular selection. The mere fact that a reference may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious unless the prior art suggested the desirability of such modification. *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements ***in the way the claimed new invention does***." See *KSR International Co. v. Teleflex Inc.*, 1741 82 USPQ2d 1385, 1396 (2007) (emphasis added). Thus, it is impermissible to simply engage in a hindsight reconstruction of the claimed invention where the reference itself provides no teaching as to why the applicant's combination would have been obvious. *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

Wilms also describes the pathway for metabolism of L-rhamnose. Wilms discloses that L-rhamnose is taken up by *E. coli* via the permease RhaT, isomerized to L-rhamnulose by the isomerase RhaA, phosphorylated by the rhamnulose kinase RhaB to rhamnulose-1-phosphate and finally hydrolyzed by the aldolase RhaD. (Wilms, p. 95, right column, lines 25-38). The products produced are consumed by other metabolic pathways. Further, Wilms discloses that the genes RhaB, A, and D form an operon controlled by the rhaBAD promoter and that expression is strictly controlled by a regulatory cascade consisting of two regulatory proteins, RhaS and RhaR. *Id.* Moreover, Wilms specifically teaches preference for the mutation in the RhaB gene because phosphorulation of L-rhamnulose by the RhaB gene is the first irreversible step in the degradation of L-rhamnose to dihydroxyacetone phosphate and L-lactaldehyde. (Wilms, p. 98, left column, lines 4-8). Wilms further teaches that this expression system takes advantage of the strictly regulated rhaBAD promoter. (Wilms, p. 95-96, right column, last sentence). Moreover, as stated in the International Preliminary Examination Report (IPER), the RhaB negative-strain is recommended especially for fermentations carried out as batch fed processes. (See English translation of IPER, p. 3, of record). Thus, Wilms disregards using any other enzyme as a potential target. Thus, Wilms and Moralejo are not combinable.

Furthermore, the isomerase RhaA catalyzes the reaction of L-rhamnose to L-rhamnulose and the rhamnulose kinase RhaB catalyzes the reaction of L-rhamnulose to rhamnulose-1-phosphate. The isomerase RhaA and the rhamnulose kinase RhaB relate to different parts of the pathway and they are totally different enzymes which catalyze totally different reactions. One skilled in the art would not substitute inactivation of a L-rhamnulose kinase with inactivation of a L-rhamnose isomerase. Furthermore, neither Wilms nor Moralejo teach or suggest the desirability of such a substitution. Thus, Wilms and Moralejo do not render the claims obvious for these additional reasons.

Furthermore, a reasonable expectation of success must be established for a proposed combination of references to render claims *prima facie* obvious. See MPEP § 2143.02 (citing *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). The reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Assuming *arguendo* the references were combined, the claims are not *prima facie* obvious over Wilms in view of Moralejo, since the Examiner has failed to provide any basis for establishing that these references can be combined as proposed with a reasonable expectation of success. Since no basis has been provided that inactivation of a L-rhamnulose kinase can be substituted by the inactivation of a L-rhamnose isomerase with a reasonable expectation of success, the Examiner has failed to establish that the claims are *prima facie* obvious.

The Examiner's contends that given the teachings in the prior art and the level of skill, "it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention." It is the Examiner's burden to establish *prima facie* obviousness and the reasonable expectation of success. "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) quoting *In re Kahn*, 441 F.3d 977, 988, (Fed. Cir. 2006). Simply stating that a skilled artisan would have had a reasonable expectation of success lacks the specificity required to support a legal conclusion of obviousness and is thus insufficient to establish *prima facie*

obviousness for this additional reason. Furthermore there would be no expectation of success that a deficiency with regard to L-rhamnose isomerase could be used based on Wilms and Moralejo teaching a mutant with inactivated L-rhamnulose kinase, because of the differences in enzymes, in reactions catalyzed, and the strictly regulated rhaBAD promoter.

Assuming *arguendo* that the Examiner had established a *prima facie* case of obviousness, a *prima facie* case of obviousness is rebuttable by evidence that the claimed invention possesses unexpectedly advantageous or superior properties. *In re Papesch*, 315 F.2d 382 (CCPA 1963).

The present invention relates to an improved method for expressing nucleic acids in prokaryotic cells using the rhaBAD promoter where surprisingly small quantities of L-rhamnose give high expression levels. (Specification, page 5, lines 1-4). The present method provides a particularly efficient reduction of rhamnose metabolization. In the present method, surprisingly, even rhamnose concentrations of as little as 0.04 g/L maintain, during induction in the fermenter, an extraordinarily high induction (see Figure 1 and Examples 5 and 8). For example, Example 8.2 shows that, in contrast to the effect of the rhamnose consumption observed by Wilms, the knocking-out of the isomerase leads to a virtually complete switching-off of the metabolization of the rhamnose in the fermenter.[1] In contrast to the low amount of rhamnose needed by the present invention, Wilms describes that a substantially higher concentration of rhamnose has to be used (Wilms, p. 100, left column and Figure 6). Figure 6 in Wilms shows that a concentration of 0.5 g/L rhamnose leads to a tailing-off of the induction after as little as 8 hours. Further, Wilms teaches that "[a]t the concentration of 0.5 g L^{-1}, the rhamnose was almost completely taken up from the cells [...]." Further Wilms teaches that only with the addition of 2 g/L rhamnose was it possible to maintain induction over a prolonged period: "A rhamnose concentration of 2 g L^{-1} seemed to be optimal." (Wilms, p. 100, left column, and Figure 6). Consequently, a sufficient expression of a gene controlled according to Wilms is not ensured at a concentration of less than 2 g/L in the fermenter. Thus, the present method differs substantially from that described by Wilms. As such, even if the Examiner had established that the claims are

[1] Please note that in Example 8.2, the difference of the cited rhamnose concentrations at the beginning and at the end of the fermentation (0.58 g/L and 0.44 g/L , respectively) must be attributed only to the dilution of the fermenter liquor (starting volume 10 L + 200 ml preculture) by glycerol feeding (2805 g glycerol solution (80%) = 2.34 L ; =1.2 g/L) and titration with ammonia water (1.0 L) to a final volume of 13.54 L (comparison of the amount of rhamnose: mstart=0.58 g/L × 10.2 L=5.9 g; mend=0.44 g/L × 13.54 L =5.9 g).

prima facie obvious over the combination of Wilms and Moralejo, this *prima facie* case would be successfully rebutted by the unexpected and superior results achieved from using the claimed process with a host cell deficient with regard to L-rhamnose isomerase when compared with the system of Wilms with a totally different enzyme, L-rhamnulose kinase. (See also specification at p. 6, lines 7-43, for further advantages of the present method).

Because Wilms and Moralejo, alone or in combination, do not teach all the claim limitations, because the reactions taught by Wilms and Moralejo are different from the claimed process, because Wilms and Moralejo are not combinable, and because assuming *arguendo* they were combinable there is no expectation of success, a *prima facie* case of obviousness has not been established. Furthermore, assuming *arguendo* that a *prima facie* case of obviousness had been established, the unexpected results successfully rebut any finding of *prima facie* obviousness. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (holding that if an independent claim is nonobvious then any claim dependent therefrom is nonobvious). Reconsideration and withdrawal of the rejection is respectfully requested.

Wilms in view of Moralejo and Israelsen

Claim 12 is rejected as being obvious under 35 U.S.C. § 103(a) over Wilms in view of Moralejo and Israelsen et al. (U.S. Patent No. 5,837,509; hereinafter "Israelsen"). Applicants respectfully traverse and urge reconsideration of the rejection for the following reasons.

The Examiner bears the initial burden of establishing *prima facie* obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

The explanations provided above under obviousness rejection over Wilms and Moralejo are equally applicable to this rejection and are incorporated herein in their entirety. As explained above, because Wilms and Moralejo, alone or in combination, do not teach all the claim limitations, because the reactions taught by Wilms and Moralejo are different from the claimed process, because Wilms and Moralejo are not combinable, and because assuming *arguendo* they were combinable there is no expectation of success, a *prima facie* case of obviousness has not been established. Furthermore, assuming *arguendo* that a *prima facie* case of obviousness had been established, the unexpected results successfully rebut any finding of *prima facie*

obviousness. Claim 12, the only claim rejected under this obviousness rejection, is a dependent claim. In *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988), the court held that if an independent claim is nonobvious then any claim dependent therefrom is nonobvious. Because the independent claim is not part of this obviousness rejection, then the claims dependent therefrom are likewise nonobvious. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

Accompanying this response is a petition for a two-month extension of time to and including December 24, 2008 with the required fee authorization. No further fee is believed due. However, if an additional fee is due, the Director is authorized to charge our Deposit Account No. 03-2775, under Order No. 12810-00091-US from which the undersigned is authorized to draw.

Respectfully submitted,

By Roberte Makowski

Roberte M. D. Makowski, Ph.D.
Registration No.: 55,421
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicants

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